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**MEMORANDUM**

SUBJECT: METHYL BROMIDE. ID No. 053201. Review of Studies on Methyl Bromide in Fumigated Dog and Rodent Diet and in Rodent Feed Containing Microencapsulated Methyl Bromide. Proposed Studies to Satisfy Dog and Rat Chronic Dietary Safety Study Requirements.

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FROM: Linnea J. Hansen, Ph.D.
Section IV, Tox. Branch I
Health Effects Division (H7509C)

Linnea J. Hansen 11/16/93

TO: Larry Schnaubelt, Manager, PM Team 72
Barry O'Keefe, Reviewer, PM Team 72
Reregistration Division (H7508W)

THRU: Marion P. Copley, D.V.M., D.A.B.T., Section Head
Section IV, Tox. Branch I
Health Effects Division (H7509C)

Marion Copley 11/15/93

Karl Baetcke, Ph.D., Branch Chief
Tox. Branch I
Health Effects Division (H7509C)

11/15/93

**CONCLUSIONS:**

1. **Summary of Results of Analysis Methods and Diet Stability Studies:** TB-I has reviewed the information submitted by the Methyl Bromide Industry Panel (MBIP) on dissipation of methyl bromide from fumigated dog and rodent feed under various conditions, release of methyl bromide from microencapsulated methyl bromide in rodent diet and attempts to improve analytical methods for detection of methyl bromide. A copy of their submission is attached to this memo. The data indicate that;(1) adding water to fumigated feed in the King Headspace Method for analysis of methyl bromide residues did not significantly improve recovery; (2) methyl bromide residues in fumigated feed underwent halogen exchange in the presence of chlorine and water to form methyl chloride with increased fumigation time; (3) addition of methyl bromide to corn oil before mixing with feed did not

improve stability; (4) methyl bromide was rapidly dissipated from dog feed containing 10% corn oil and fumigated with methyl bromide although by 45 - 60 min., rate of loss plateaued; (5) methyl bromide levels detected in rodent diet containing microencapsulated methyl bromide were relatively stable when stored at room temperature.

2. **Discussion of Study Design for Chronic Toxicity Testing in Rat and Dog:** The MBIP proposed that the following studies be conducted in lieu of chronic dietary studies using fumigated feed in rat and dog due to instability of methyl bromide in fumigated feed and because California and U.S. EPA have different chronic toxicity data requirements:

a. Rat chronic toxicity study (83-1a) using microencapsulated methyl bromide in the diet;

b. Dog chronic toxicity study (83-1b) performed by inhalation exposure and combined with a pharmacokinetic studies to allow "bridging" between dietary and inhalation exposure.

TB-I will not accept a chronic dog inhalation study with "bridging" studies as an acceptable alternative to a dietary safety study. Based on the submitted information and on a previous conservative estimate of average daily human consumption of methyl bromide residues by the Agency (0.05 ppm), it would appear that a dietary dog safety study using fumigated feed with 10% corn oil at a dose that would give a safety factor of at least 100 for human consumption (eg. >5 ppm in dog feed) is feasible. TB-I notes that the estimate for human dietary exposure may overstate actual exposure because of continual dissipation of methyl bromide expected to occur between aeration and actual consumption.

If adequate levels of methyl bromide can be retained in rat diet, the rat may also be tested using fumigated diet; a fumigated feed safety study is strongly preferred by TB-I. A toxicity study using microencapsulated methyl bromide in diet may be substituted if preliminary studies show that (1) dissipation of methyl bromide from fumigated feed after 24 hrs gives inadequate margin of safety (eg. for rat, < 2.5 ppm in diet), (2) bioavailability of microencapsulated methyl bromide can be demonstrated and (3) microencapsulated methyl bromide is not excessively irritating to the gastrointestinal tract of rats. These issues are discussed in detail below under "Discussion".

TB-I is concerned about the apparent delays by the MBIP in resolving problems associated with conduct of the chronic dietary studies since the Data Call-In requiring dietary safety studies was issued two years ago and since meeting with the Agency to discuss the chronic data requirements 3½ years ago. The Data

Call-In (9-20-91) was considered the Agency's final position on these data requirements. It is noted that in a letter dated 11-25-92 from the MBIP, preliminary testing for the dietary safety studies still had not been initiated. The MBIP should initiate preliminary studies and chronic testing as soon as possible.

TB-I does not consider a meeting with the MBIP to be necessary at this time. The comments in this memo should provide adequate guidance for conducting chronic dietary safety studies in dog and rat. TB-I notes its strong preference for a rat dietary safety study using fumigated feed but final decision on method of dietary administration in rat is at the discretion of the MBIP pending results of the appropriate preliminary studies as described elsewhere in this memo.

**ACTION REQUESTED:**

On behalf of the Methyl Bromide Industry Panel, The Chemical Manufacturers' Association submitted for review results of preliminary studies on analysis methods and stability of methyl bromide in fumigated dog and rodent diet, in corn oil and of microencapsulated methyl bromide in rodent diet (MRID No. 429183-01; attached to this memo). These studies (non-guideline) were performed in an attempt to improve analytical methods for methyl bromide in feed and increase retention of methyl bromide residues in laboratory animal feed for conducting dietary safety studies. Some data was previously submitted on dietary fumigation and microencapsulated methyl bromide (see memo from L. Hansen to L. Schnaubelt dated 2-3-93 for review).

The Methyl Bromide Industry Panel proposed alternatives to studies using fumigated diet for chronic data testing of methyl bromide and requested a meeting with the Agency to discuss their proposal.

**DISCUSSION:**

Background: Chronic dietary safety studies in rat and dog using fumigated feed are required by the U.S. EPA for methyl bromide to support tolerances for fumigated food commodities. Current tolerances (40 CFR 180.199) are based on inorganic bromide ion residues. In correspondence between A. Lindsay, RD and V. White, MBIP, 7-7-89, the Agency informed the Registrant that the inorganic bromide tolerances would be replaced with tolerances for residues of methyl bromide *per se* once the information became available. These studies have recently been received by Chemistry Branch II and preliminary examination of the data indicates that methyl bromide residues are identified in many of these commodities after 24 - 48 hrs of aeration.

On September 20, 1991 the Agency issued a Data Call-In for methyl bromide in which chronic dietary safety studies were

required in dog and rat. The toxicology data requirements were outlined in a memorandum from M. Copley to L. Rossi dated 6-12-91 (see attached copy). Testing of animals fed diets fumigated with methyl bromide was chosen because it best approximates potential human dietary exposure and provides information on methyl bromide residues per se as well as degradation products of methyl bromide following fumigation. Safety studies (as opposed to standard toxicity studies) were selected because of anticipated difficulty achieving constant, high concentrations of methyl bromide in fumigated feed. Gavage is not considered an appropriate route of administration for this compound because of gastric irritation. Methyl bromide has been shown to produce forestomach tumors in rats which regress after termination of dosing.

(Note: The dietary safety studies required in the Data Call-In supercede all previous considerations of alternative study designs by the Agency. In May 1990, the Agency met with the MBIP and discussed the chronic feeding studies. The MBIP suggested that an inhalation study in dogs, together with pharmacokinetic bridging studies to compare metabolism following oral vs. inhalation exposure, might be an alternative to a dietary study. At that time HED responded (memo to D. Mackey dated 7-25-90) that: "...bridging studies are being considered in an attempt to justify not carrying out long-term rodent studies by the oral route. If it can be shown that the metabolism and kinetics of MeBr, when absorbed following oral and inhalation exposure, are similar by producing similar metabolites and distribution patterns we can use the inhalation studies.")

EPA previously reviewed the following submissions from the MBIP pertinent to conduct of chronic dietary toxicity studies: protocol for a chronic dog dietary study, pharmacokinetic studies, bioavailability of microencapsulated methyl bromide and a Japanese chronic rat feeding study (not referenced in this memo).

Use of Dog Inhalation Study and Pharmacokinetic Study to Substitute for Feeding Study: TB-I will not accept a chronic dog inhalation study with "bridging" studies as an appropriate substitute for a chronic dietary study. This reviewer feels that an inhalation study with bridging is not an appropriate alternative because of (1) the potentially significant differences in metabolism and target organ toxicity between the oral and inhalation routes for an irritating, reactive vapor such as methyl bromide and (2) technical difficulty of performing the study. Furthermore, if significant differences in metabolism were observed following oral vs. inhalation exposure, a dietary study would still be required. There is adequate data already available on toxicity from long term exposure via inhalation which can be used for occupational risk evaluation.

Feasibility of Fumigated Dietary Safety Studies in Dogs:

TB-I believes that the submitted information, along with a previous estimate of average human dietary exposure to methyl bromide, indicates that an adequate dietary safety study in dogs is feasible using fumigated feed. In a memo dated 8-29-91 from R. Perfetti to W. Burnam and L. Rossi (see attached copy), a human baseline level for average chronic dietary exposure to methyl bromide residues was estimated at 0.05 ppm. Based on preliminary examination of multiple post-harvest crop residue data recently received in Chemistry Branch II of HED, this number is still considered a conservative estimate (personal communication, R. Perfetti). TB-I notes that this value may overestimate actual human exposure since delays of days or weeks between aeration and actual consumption can be expected. Refinement of this estimate will follow review of residue studies.

Commonly used ppm-to-mg/kg/day conversion factors (see attached table) can be used to equate ppm dose among species. Since the same conversion factor (0.025 mg/kg/day per ppm) is used for human diet as for dogs receiving dry meal, 0.05 ppm with a safety factor of at least 100 can be used to give a minimum dietary dose requirement of about 5 ppm methyl bromide for a safety study in dogs. This translates to 0.125 mg methyl bromide/kg body wt./day in dog and rodent studies.

The recently submitted data on diet fumigation showed that dog feed containing 10% corn oil and fumigated to approximately 1000 ppm rapidly lost methyl bromide during aeration (see Table V of the submission, attached). However, this graph also showed that the rate of methyl bromide loss from fumigated feed plateaued between 45 to 60 min. After 100 minutes of aeration diet still contained 8 ppm, which would give at least a 100-fold margin of safety.

If dogs were administered diet after 45 - 60 min. aeration, between 8 and 20 ppm methyl bromide would be present in the diet and MOEs for human dietary exposure would be considered adequate. A minimum daily dietary concentration could be estimated; as long as this (and the maximum level) could be determined, accurate daily dietary intake would not be necessary. Since dogs are fed once daily and tend to consume their daily ration rapidly after administration, there would be relatively little additional dissipation of methyl bromide. Conversion of methyl bromide to methyl chloride would be minimal in this time (TB-I does not consider limited conversion to methyl chloride to be problematic since it may reflect similar conversion in foods consumed by humans and since toxicity would not be expected to be significantly greater for methyl chloride).

Administration of fumigated feed at low concentrations should not cause gastric irritation as observed after single dosing with methyl bromide in corn oil in gelatin capsules. It is noted that palatability/irritation of methyl bromide in diet

has not been adequately tested in dogs; only one study using a single dose of methyl bromide dissolved in corn oil and administered in gelatin capsules was conducted (MRID 416735-01). The low dose required to achieve adequate safety testing (≥0.125 mg/kg/day) is not anticipated to produce irritation in dogs.

Comments on Study Design for Dog Dietary Safety Study: The following points pertaining to study design are noted: (1) In contrast to a standard 3-dose toxicity study, the safety study may have only one dose and is intended to obtain an acceptable safety factor (at least 100) for human dietary consumption. Determination of a LEL is not required. A safety study was required in recognition of the difficulty obtaining constant high dose levels in fumigated feed for a conventional multi-dose toxicity study; (2) Because of the difficulty maintaining a constant dose of methyl bromide with fumigated feed a minimum dose level and a range of rather than exact, constant doses may be described; (3) Since only one dose is used the number of dogs should be increased from the usual 4/dose/sex to 8 - 10; (4) Although addition of corn oil to dog feed did not prevent the rapid loss of methyl bromide residues during the first hour of aeration, the data did not indicate whether low levels of methyl bromide persist longer in oil-containing diet than in standard diet. Oil-treated diet may be preferable for retaining low levels of methyl bromide during feeding.

Dietary Dosing of Rats with Fumigated Feed vs. Diet Containing Microencapsulated Methyl Bromide: An adequate dietary level of methyl bromide residues in fumigated feed is more difficult to control in rats due to their intermittent food consumption patterns. This is still the preferred route of administration for the rat chronic dietary study if adequate levels of methyl bromide residue levels persist in rat feed during the day. Using the same procedure and conversion numbers as described for dog, dietary level of at least 2.5 ppm methyl bromide would be required for a rat safety study (equivalent to 5 ppm in humans and dogs). Administration in diet using microencapsulated methyl bromide may be performed if (1) minimum levels of methyl bromide in diet of approximately 2.5 ppm cannot be achieved (2) bioavailability of microencapsulated methyl bromide and an adequate bioavailable dose demonstrated, and if (3) preliminary studies show that administration of microencapsulated methyl bromide is not excessively irritating to the GI tract.

Comments on Study Design for Rat Dietary Study: (1) The same comments as for dog apply to a rat safety study using fumigated feed; (2) If a study using microencapsulated methyl bromide is selected, several dose levels should be tested since relatively constant doses may be administered.